REMARKS

Claims 1-7, 9-23, and 26-27 are pending in the application. Claims 28-37 have been cancelled as drawn to a non-elected invention. Claims 8 24, and 25 have also been cancelled. Claims 1-7, 12, 15-23, and 27 have been amended herein. The amendments to these claims are supported throughout the specification and the claims as originally filed. Thus, no new matter has been added.

Claim Rejections

Double Patenting

Claims 1, 2, 4, 6, 16, 17, 19, 21, and 22 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-57 of United States Patent Number 6,268,142 ("the '142 patent"). Applicants traverse.

Independent, claims 1 and 16 (and the claims 2, 4, 6, 17, 19, 21 and 22 which depend therefrom) have been amended to incorporate the limitations of original claims 8 and 25 respectively. Claims 1 and 16, as amended herein, require the administration of an inducer to the test subject or to the cells obtained from the test subject prior to or concomitant with of observing the biomarkers. Claims 48-57 of the '142 do not contain all the limitation of claim 1 and 16 as amended, therefore Applicants assert that claims 1 and 16 (and the claims that depend therefrom) of the instant application are patentably distinct from claims 48-57 of the '142 patent. Thus, Applicants assert that this rejection should be withdrawn.

35 U.S.C. § 102

Claims 1-8 and 16-27 have been rejected as being anticipated by Duff *et al.* (U.S. Patnet No. 6,268,142) ("Duff"). According to the Examiner, Duff teaches a method for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype.

Applicants have amended independent claims 1 and 16 to require administering an inducer to the test subject prior to or concomitant with observing the biomarker. The Examiner contends that a promoter as used in Duff can be considered an inducer. Applicants disagree. " Duff does not specifically define the term promoter. Duff defines "transcriptional regulatory sequence" as "a generic term used...to refer to DNA sequences, such as initiation signals,

enhancers, and *promoters*, which induce or control transcription of protein coding sequences with which they are *operably* linked." Duff, col. 12, lines 60-64. Thus, a skilled artisans reading Duff would give the term promoter the plain meaning-- a DNA sequence that controls to initiates transcription of mRNA. *In contrast,* the inducers referred to in the present application, includes exercise, irritants that evoke an inflammatory response, substances that activate IL-1 production, mitogens and cytokines. As Duff does not teach or suggest the inducers as specifically defined in the present application, Duff does not anticipate the invention as claimed. Applicants request that this rejection be withdrawn.

35 U.S.C. § 103

A. Duff in view of Girten

Claims 9-10 have been rejected as being obvious over Duff in view of Girten *et al.* (U.S. Patent Number 5,760,001) ("Girten"). Applicants traverse.

As a preliminary matter there is no suggestion to combine Duff and Girten to produce the claimed invention. Furthermore, even if combined (which Applicants do not believe is proper) these references do not teach or suggest the invention as presently claimed.

According to the Examiner, Duff teaches the method of claims 1-8 and 16-27 however Duff does not teach a method of causing exercise-induced stress with a treadmill stress test, or induction of cytokine expression by any other method. (claims 9 and 10). For the reason discussed above Duff does not anticipated independent claim 1 as amended and therefore can not anticipate the claims that depend therefrom (*i.e.*, 9 and 10)

Girten does not cure theses deficiencies. Girten teaches a method of "restraining" the biological activity of a cytokine to treat conditions resulting from elevated cytokine production, including disuse deconditioning, diabetes and glomerulonephritis, as well as cytokine-mediated organ damage resulting from organ transplants or chemotherapy. Thus Girten teaches that a reduction of cytokine production may be useful in treating particular disease condition associated with increases cytokine production. Girten does not teach a method of *identifying* a substance that reduces a biological response by observing a biomarker in a subject having exercise induced stress as required by claims 9 and 10.

Claims 11-15 have been rejected as being obvious over Duff in view of Hallahan *et al.* (U.S. Patent Number 5,962,424) ("Hallahan"). Applicants traverse. There is no suggestion to combine Duff and Hallahan to produce the claimed invention. Furthermore, even if combined (which Applicants do not believe is proper) these references do not teach or suggest the invention as presently claimed.

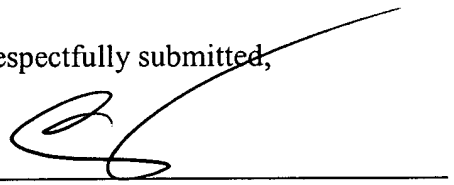
For the reason discussed above Duff does not anticipated independent claim 1 as amended and therefore cannot anticipate the claims that depend therefrom (*i.e.*, 11-15).

Hallahan does not cure theses deficiencies. Hallahan teaches a method for specifically targeting therapeutic and diagnostic agents to tumor vasculature by inducing E-selectin or L-selectin expression by x-ray irradiation or an oxidient. Hallahan, also teaches that monosodium urate crystal induces arthritis. Hallahan does not teach a method of *identifying* a substance that reduces a biological response by observing a biomarker such as in a subject having an irritant (such as monosodium urate crystals) induced inflammatory response as required by claims 11-15.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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AMENDMENTS

In the Claims:

1. (Currently amended) A method for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype, said method comprising the steps of:

~~a) genotyping at least one subject to identify a test subject, wherein said test subject is a subject having an inflammatory disease-associated genotype;~~

a~~-b~~) observing in ~~said~~ a test subject having an inflammatory disease-associated genotype ~~at least one~~ a biomarker;

b~~e~~) contacting said test subject with a test substance;

c~~d~~) observing again in said test subject said ~~at least one~~ biomarker; and,

d) administering an inducer to the test subject prior to or concomitant with observing said biomarker,

wherein a change in said ~~at least one~~ biomarker from an inflammatory disease-associated phenotype to a non-inflammatory disease-associated phenotype identifies a test substance that is likely to prevent or diminish the specific biological response in a subject having said inflammatory disease-associated genotype.

2. (Currently amended) A method of claim 1, wherein said subject ~~having an inflammatory disease-associated genotype~~ has at least one inflammatory disease-associated allele ~~from one of the following chromosomal regions:~~ selected from the group consisting of IL-1A, IL-1B, IL-1RN, TNFA and IL-13.

3. (Currently amended) A method of claim 1, wherein said subject ~~having an inflammatory disease-associated genotype~~ has at least one inflammatory disease-associated allele from the IL-1 44112332 haplotype or the IL-1 33221461 haplotype.

4. (Currently amended) A method of claim 1, wherein said subject ~~having an inflammatory disease-associated genotype~~ has at least one allele selected from the group consisting of allele 1 of IL-1A (+4845), allele 4 of IL-1A (222/223), allele 4 of IL-1A (gz5/gz6), allele 1 of IL-1A (-889), allele 2 of IL-1B (-511) , allele 3 of gaat.p33330, allele 3 of Y31, allele 2 of IL-1RN (+2018), allele 2 of IL-1RN (1731), allele 2 of IL-1RN (1812), allele 2 of IL-1RN (1868), allele 2 of IL-1RN (1887), allele 2 of IL-1RN (8006), allele 2 of IL-1RN (8061), allele 2 of IL-1RN (9589), allele 2 of IL-1A (+4845), allele 3 of IL-1A (222/223), allele 3 of IL-1A (gz5/gz6), allele 2 of IL-1A (-889), allele 1 of IL-1B (-511), allele 4 of gaat.p33330, allele 6 of Y31, allele 1 of IL-1RN (+2018), allele 2 of IL-1B (+6912), allele 2 of TNFA (-308), allele 2 of TNFA (-238), and allele 2 of IL-13 (+2581).

5. (Currently amended) A method of claim 1 ~~2~~, wherein said inflammatory disease-associated genotype is associated with a predisposition to a disease selected from the group consisting of periodontal disease, coronary artery disease, atherosclerosis, Alzheimer's disease, osteoporosis, insulin-dependent diabetes, diabetic retinopathy, end-stage renal disease, diabetic nephropathy, hepatic fibrosis, alopecia areata, Graves' disease, Graves' opthalmopathy, extrathyroid disease, systemic lupus erythematosus, lichen sclerosis, rheumatoid arthritis, juvenile chronic arthritis, gastric cancer, ulcerative colitis, asthma, multiple sclerosis, interstitial lung disease, idiopathic pulmonary fibrosis, sepsis and acne.

6. (Currently amended) A method of claim 1, wherein said subject ~~having an inflammatory disease-associated genotype~~ is homozygous for an allele selected from the group consisting of: allele 1 of IL-1A (+4845), allele 4 of IL-1A (222/223), allele 4 of IL-1A (gz5/gz6), allele 1 of IL-1A (-889), allele 2 of IL-1B (-511) , allele 3 of gaat.p33330, allele 3 of Y31, allele 2 of IL-1RN (+2018), allele 2 of IL-1RN (1731), allele 2 of IL-1RN (1812), allele 2

of IL-1RN (1868), allele 2 of IL-1RN (1887), allele 2 of IL-1RN (8006), allele 2 of IL-1RN (8061), allele 2 of IL-1RN (9589), allele 2 of IL-1A (+4845), allele 3 of IL-1A (222/223), allele 3 of IL-1A (gz5/gz6), allele 2 of IL-1A (-889), allele 1 of IL-1B (-511), allele 4 of gaat.p33330, allele 6 of Y31, allele 1 of IL-1RN (+2018), allele 2 of IL-1B (+6912), allele 2 of TNFA (-308), allele 2 of TNFA (-238), and allele 2 of IL-13 (+2581).

7. (Currently amended) A method of claim 2, wherein said ~~at least one~~ biomarker is selected from the group consisting of: electrocardiogram parameters, pulmonary function, core body temperature, blood or urine IL-1α levels, blood or urine IL-1β levels, blood levels of soluble IL-1 receptors, blood or urine IL-13 levels, blood or urine IL-6 levels, blood or urine TNFα levels, blood levels of stable eicosanoids, nitric oxide levels, white blood cell count, blood lipid levels, red blood cell count, platelet count, blood iron levels, blood zinc levels, blood neopterin level, blood reactive oxygen species, blood levels of C reactive protein, blood levels of fibrinogen, steroid hormone levels, standard urine parameters, size of skin erythema, and duration of skin erythema.

8. (Cancelled)

9. A method of claim 1, wherein said inducer comprises exercise sufficient to cause exercise induced stress.

10. A method of claim 9, wherein said exercise is a treadmill stress test.

11. A method of claim 1, wherein said inducer comprises a subcutaneous injection of an irritant.

12. (Currently amended) A method of claim 11, wherein said irritant induces a ~~strong~~ monocytic inflammatory response ~~that is minimally influenced by an antibody response that may result from previous exposure to various antigens.~~

13. A method of claim 11, wherein the irritant is urate crystals.

14. A method of claim 11 wherein the irritant is monosodium urate crystals.

15. (Currently amended) A method of claim 11, wherein said at least one biomarker includes the dimensions ~~and/~~or duration of skin erythrema resulting ~~form~~ from said subcutaneous injection.

16. (Currently amended) A method for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype, said method comprising the steps of:

a) ~~genotyping at least one subject to identify~~ providing a cell from a test subject, ~~wherein said test subject is a subject~~ having an inflammatory disease-associated genotype;

b) observing in said cells ~~obtained from said test subject~~, or a cells propagated therefrom, ~~at least one~~ a biomarker;

c) contacting said cells ~~obtained from said test subject, or cells propagated therefrom,~~ with a test substance;

d) observing again in said cells ~~obtained from said test subject, or cells propagated therefrom, said at least one~~ said biomarker; and

e) contacting said cells with an inducer prior to or concomitant observing said biomarker,

wherein a change in said ~~at least one~~ biomarker from an inflammatory disease-associated phenotype to a non-inflammatory disease-associated phenotype identifies a test substance that is likely to prevent or diminish the specific ~~immune~~ biological response in a subject ~~having said inflammatory disease-associated genotype~~.

17. (Currently amended) A method of claim 16, wherein said subject having an inflammatory disease-associated genotype has at least one inflammatory disease-associated allele ~~from one of the following chromosomal regions:~~ selected from the group consisting of IL-1A, IL-1B, IL-1RN, TNFA and IL-13.

18. (Currently amended) A method of claim 16, wherein said subject ~~having an inflammatory disease-associated genotype~~ has at least one inflammatory disease-associated allele from the IL-1 44112332 haplotype or the IL-1 33221461 haplotype.

19. (Currently amended) A method of claim 16, wherein said subject ~~having an inflammatory disease-associated genotype~~ has at least one allele selected from the group consisting of allele 1 of IL-1A (+4845), allele 4 of IL-1A (222/223), allele 4 of IL-1A (gz5/gz6), allele 1 of IL-1A (-889), allele 2 of IL-1B (-511) , allele 3 of gaat.p33330, allele 3 of Y31, allele 2 of IL-1RN (+2018), allele 2 of IL-1RN (1731), allele 2 of IL-1RN (1812), allele 2 of IL-1RN (1868), allele 2 of IL-1RN (1887), allele 2 of IL-1RN (8006), allele 2 of IL-1RN (8061), allele 2 of IL-1RN (9589), allele 2 of IL-1A (+4845), allele 3 of IL-1A (222/223), allele 3 of IL-1A (gz5/gz6), allele 2 of IL-1A (-889), allele 1 of IL-1B (-511), allele 4 of gaat.p33330, allele 6 of Y31, allele 1 of IL-1RN (+2018), allele 2 of IL-1B (+6912), allele 2 of TNFA (-308), allele 2 of TNFA (-238), and allele 2 of IL-13 (+2581).

20. (Currently amended) A method of claim 16, wherein said inflammatory disease-associated genotype is associated with a predisposition to a disease selected from the group

consisting of ~~one or more of the following:~~ periodontal disease, coronary artery disease, atherosclerosis, Alzheimer's disease, osteoporosis, insulin-dependent diabetes, diabetic retinopathy, end-stage renal disease, diabetic nephropathy, hepatic fibrosis, alopecia areata, Graves' disease, Graves' opthalmopathy, extrathyroid disease, systemic lupus erythematosus, lichen sclerosis, rheumatoid arthritis, juvenile chronic arthritis, gastric cancer, ulcerative colitis, asthma, multiple sclerosis, interstitial lung disease, idiopathic pulmonary fibrosis, sepsis and acne.

21. (Currently amended) A method of claim 16, wherein said subject ~~having an inflammatory disease-associated genotype~~ is homozygous for an allele selected from the group consisting of: allele 1 of IL-1A (+4845), allele 4 of IL-1A (222/223), allele 4 of IL-1A (gz5/gz6), allele 1 of IL-1A (-889), allele 2 of IL-1B (-511) , allele 3 of gaat.p33330, allele 3 of Y31, allele 2 of IL-1RN (+2018), allele 2 of IL-1RN (1731), allele 2 of IL-1RN (1812), allele 2 of IL-1RN (1868), allele 2 of IL-1RN (1887), allele 2 of IL-1RN (8006), allele 2 of IL-1RN (8061), allele 2 of IL-1RN (9589), allele 2 of IL-1A (+4845), allele 3 of IL-1A (222/223), allele 3 of IL-1A (gz5/gz6), allele 2 of IL-1A (-889), allele 1 of IL-1B (-511), allele 4 of gaat.p33330, allele 6 of Y31, allele 1 of IL-1RN (+2018), allele 2 of IL-1B (+6912), allele 2 of TNFA (-308), allele 2 of TNFA (-238), and allele 2 of IL-13 (+2581).

22. (Currently amended) A method of claim 16, wherein said ~~at least one~~ biomarker is selected from the group consisting of: IL-1α production, IL-1β production, prostanoid production, TNFα production, large-scale gene transcript level analysis, and large-scale protein level analysis.

23. (Currently amended) A method of claim 16, wherein said cells ~~obtained from said test subject, or cells propagated therefrom, are~~ is an immune cells.

24. (Cancelled).

25. (Cancelled)

26. A method of claim 16, wherein said inducer is a substance known to activate IL-1 production in monocytes or macrophages.

27. (Currently amended) A method of claim 16, wherein said inducer ~~comprises one or more of the following:~~ is selected from the group consisting of a lipopolysaccharide, concanavalin A, phytohemagglutinin, phorbol myristic acid (PMA), a calcium ionophore, interferon gamma, interleukin-12, interleukin-1, TNFα, UV radiation, and ionizing radiation.

28. - 37. (Cancelled)